--61. (Amended) The method of claim 57, wherein the primary amine group which is linked to the third oligonucleotide is a C-7 amine.--

D12

--62. (Amended) The method of claim 57, wherein the third oligonucleotide is immobilized on a solid support.--

--64. (Amended) The method of claim 57, wherein the third oligonucleotide (1) is immobilized; (2) comprises the sequence TACGGACGGAAACTGTTTTTTTTTTT (SEQ ID NO:4); (3) is linked to 6-(fluorescein-6-carboxamido) hexanoate at its 5' terminus, and (4) is linked to a C-7 amine at its 3' terminus.--

D13

--65. (Amended) The method of claim 57, wherein the primer in step (B)(1) has the sequence AGGATCAACAACAACCAGTA (SEQ ID NO:6).--

--66. (Amended) The method of claim 57, wherein the primer in step (B)(2) has the sequence ATCGTCCTGGGCTTTCGCAA (SEQ ID NO:7).--

A mark up copy of the amendments to the claims is attached hereto as **Exhibit 2**.

REMARKS

Claims 19-68 are pending in the subject application. Applicants have hereinabove canceled claim 37 and amended claims 20, 21, 26, 29, 30, 35, 36, 39, 41, 43, 44, 46, 47, 48, 49, 50, 52, 53, 54, 57, 58, 59, 60, 61, 62, 64, 65, and 66 to insert SEQ ID NO.s where appropriate, and to make it clear which oligonucleotide is being claimed in certain dependent claims, as requested by the

Examiner. Support for the amendment to claim 36 can be found in the specification at page 10, lines 10-17. Applicants contend that the amendments to the specification and claims do not involve any issue of new matter. Applicants respectfully request entry of this Amendment such that claims 19-36 and 38-68 will be pending.

A November 30, 2002 Final Office Action was issued in connection with U.S. Serial No. 09/362,394 of which the above-identified application is a CPA. In the November 30, 2002 Final Office Action The Examiner stated that claims 1-18 were canceled, new claims 19-68 were added in Paper No. 12 submitted 9/17/01, and that claims 19-68 are presently under examination.

The Examiner stated that as a result of the amendment to the specification and the new claims presented in Paper No. 12, this application is no longer in compliance with the sequence rules, and, in particular, sequences embedded in the text of new paragraphs presented in the amendment (e.g. at page 9 and page 14) and in new claims 20, 21, 26, 29, 30, 35, 37, 39, 41, 43, 46, 47, 52, 53, 54, 58, 59, 64, 65, and 66 are not accompanied by the appropriate SEQ ID NO's as is required by 37 C.F.R. §1.821(d). The Examiner stated that applicant must supply the SEQ ID NO's in any response to this action.

In response, applicants have amended the specification and claims to include sequence identifiers where necessary.

The Examiner stated that claims 19-41 are drawn to oligonucleotides; claims 42 and 43 are drawn to an oligonucleotide composition; claims 44-68 are drawn to methods for identifying hepatitis B viral nucleic acid sequences. The Examiner stated that claims 43, 53, 54, 65, and 66 are indefinite

in reciting "has the sequence..." and that it remains unclear whether applicant intends "has" to represent open language, equivalent to "comprising," or closed language, equivalent to "consisting of. "The Examiner stated that in the absence of amendment or clarification of what applicant intends to claim, and consistent with the practice of giving claims their broadcast reasonable interpretation, the recitation of "has" has been interpreted as open language.

The Examiner stated that claims 46-50, and 52, and claims 58-62, and 64 are indefinite in reciting "the oligonucleotide" without clear antecedent in independent claims 44 and 57, respectively, and that claims 44 and 57 each recite "oligonucleotide"more than once, making it unclear which oligonucleotide is being claimed in the dependent claims.

In response, without conceding the correctness of the Examiner's position, applicants have hereinabove amended claims 44, 46-50, 52, 57-62, and 64 to more clearly point out which nucleotide is being referred to in the dependent claims.

The Examiner stated that claims 19-68 are rejected under 35 U.S.C. §103(a) as being unpatentable over WO 97/40193 to Stuyver et al., of record, essentially for reasons of record in rejecting claims 1-18 in the previous Office Action.

The Examiner stated that applicant has argued that the cited references at most describes PCR amplification of samples which may then be screened using labeled probes and points to examples 1 and 2 on pages 33 and 34. The Examiner stated that applicant argues that the claimed invention differs in that it relates to the labeling of PCR amplified viral nucleic acids by using labeled PCR primers, where the reference uses labeled probes;

that the claimed invention relates to immobilized probes, while the reference suggests using mobile probes; that the claims recite specific oligonucleotide sequences with particular lengths that are not suggested in the cited reference; that the claims recite particular labels, viz. Texas red and 6-FAM, not disclosed in the cited reference.

The Examiner stated that these arguments have been considered but not found persuasive. The Examiner stated that Stuyver et al. disclose labeled primers, labeled target DNA, and immobilized probes (see e.g., page 13, lines 8-22; page 16, lines 5-20), and, further, none of the instant claims are limited to specific length oligonucleotides; even the claims that recite a specific sequence recite open language, either "comprising" or "has" that allows for longer oligonucleotides. While Stuyver et al. does not specifically name Texas red and 6-FAM, it is noted that not all the instant claims are limited to the labels Texas red and/or 6-FAM, in the absence of persuasive argument or evidence to the contrary, any label of choice is deemed to be obvious over the teaching of Stuyver et al. to label the oligonucleotides to be used in the disclosed assays.

In response, applicants assert that the choice of any label is not obvious over Stuyver et al. Applicants note that MPEP §2143 states the Examiner must establish a prima facie case of obviousness, including showing "there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of skill in the art, to modify the reference". Applicants respectfully assert that the Examiner has not shown the suggestion or motivation to attach "any label of choice" (i.e. any thing attachable to an oligonucleotide) to the oligonucleotides in question. Applicants request that the Examiner specifically point out the suggestion

or motivation to attach fluorescent labels. Applicants further note that Stuyver at al. does not explicitly or implicitly teach fluorescent labels as a subgenus, nor any individual species as claimed by applicants. Moreover, applicants note that the Examiner has not shown that any fluorescent molecules can be used as labels and reasonably expect success. In support of applicant's assertion, it is noted that different fluorescent dyes offer different absorption, emission, molecular weight, photostability, and importantly, environmental sensitivity of fluorescence e.g. solvent polarity, pH (see Introduction to Fluorescence Techniques in "Handbook of Fluorescence Probes and Research Techniques", Molecular Probes, 8th Ed. - **Exhibit 3**). Moreover, different fluorescent dyes can alter the behavior of PCR, e.g. mobility retardation problems (see Hahn et al. (2001) - **Exhibit 4**). Applicants therefore request that the Examiner reconsider and withdraw the 35 U.S.C. §103(a) rejection of claims 19-35 and 38-68.

Also in response, applicants further note that according to MPEP §2143 the prior art reference must teach or suggest all the claim limitations. Applicants note that Stuyver at al. fails to teach all characteristics of the claims detailed below.

Claims 19-25: there is no suggestion or teaching in Stuyver et al. of an oligonucleotide which corresponds to a portion of a wildtype human hepatitis B virus surface antigen nucleic acid and which is linked to a fluorescent dye at its 5' terminus, and linked to a primary amine group at its 3' terminus.

Claim 26: there is no suggestion or teaching in Stuyver et al. of an immobilized oligonucleotide comprising SEQ ID NO:4 that is linked to 6-(fluorescein-6-carboxamido) hexanoate at its 5' terminus, and is linked to a C-7 amine at its 3' terminus.

Claims 27-34: there is no suggestion or teaching in Stuyver et al. of an oligonucleotide that is comprised of a portion of a human hepatitis virus and is linked to a fluorescent dye at its 5' terminus and to a primary amino group at its 3' terminus.

Claim 35: there is no suggestion or teaching in Stuyver et al. of an immobilized oligonucleotide comprising SEQ ID NO:5 that is linked to 6-(fluorescein-6-carboxamido) hexanoate at its 5' terminus, and is linked to a C-7 amine at its 3' terminus.

Claim 36: there is no suggestion or teaching in Stuyver et al. of an oligonucleotide which has a sequence which corresponds to a portion of a nucleic acid which encodes human hepatitis B virus surface antigen, wherein the sequence is AGGATCAACAACAACCAGTA (SEQ ID NO:6), and is linked at its 5' terminus to a biotin group.

Claims 38-41: there is no suggestion or teaching in Stuyver et al. of an oligonucleotide which is complementary to a nucleic acid which encodes human hepatitis B virus surface antigen and is linked at its 5' terminus to a fluorescent dye, nor where the dye is specifically Texas red.

Claims 42-43: there is no suggestion or teaching in Stuyver et al. of a composition comprising two oligonucleotides, one of which corresponds to a portion of a nucleic acid which encodes human hepatitis B virus surface antigen and is linked at its 5' terminus to a biotin group, and the other of which has a sequence which is complementary to a nucleic acid which encodes human hepatitis B virus surface antigen, and is linked at its 5' terminus to a fluorescent dye, nor where the dye is specifically Texas red.

Claims 44-56: there is no suggestion or teaching in Stuyver et al. of a method for identifying a human hepatitis B virus surface antigen mutant 145 which comprises amplifying the nucleic acid in a reaction using two primers, wherein one primer is linked at its 5' terminus to biotin and the second is linked at its 5' terminus to a fluorescent dye.

Claims 57-68: there is no suggestion or teaching in Stuyver et al. of a method for identifying a wildtype human hepatitis B virus surface antigen which comprises amplifying the nucleic acid in a reaction using two primers, wherein one primer is linked at its 5' terminus to biotin and the second is linked at its 5' terminus to a fluorescent dye.

Applicants therefore request that the Examiner reconsider and withdraw the 35 U.S.C. §103(a) rejection of claims 19-36 and 38-68.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone at the number provided below.

No fee, other than the enclosed filing fee of $1766.00, is deemed necessary in connection with the filing of this Preliminary Amendment. However, if any such fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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Mark Up copy of Amendments to the Specification

The paragraph starting at page 9, line 14 has been amended as follows:

--One of the applications of the present invention is the detection of the human hepatitis B virus surface antigen mutant 145 (Glycine to Arginine) using a solid glass supports device. In the present invention, further modifications have been added to two oligonucleotides (listed herein): 5'-TACGGACGGAAACT-3' (SEQ ID NO:3), and 5'-TACGGACAGAAACT-3' (SEQ ID NO:1), both located from position 582 to 595 as referred to the wild type human hepatitis B virus genome. These modifications include a fluorescent dye, 6-(fluorescein-6-carboxamido) hexanoate (6FAM), at its 5' terminus and a primary amine group at its 3' terminus. The resulting oligonucleotides that are immobilized on solid glass supports have the following structure: 5'-(6FAM)TACGGACGGAAACTGTTTTTTTTTTT (C-7 amine)-3' (SEQ ID NO:4), and 5'-(6FAM)TACGGACAGAAACTGTTTTTTTTTTT (C-7 amine)-3' (SEQ ID NO:5), and the second oligonucleotide contains the mutation G to A (position 8) leading to change at amino acid 145 (Glycine to Arginine) of human hepatitis B virus surface antigen. There is also an inclusion of a poly-T (underlined) as a synthetic linker aiming at facilitating the subsequent hybridization reaction with target human viral DNA sequences from serum samples.--

The paragraph starting at page 14, line 31, has been amended as follows:

--As a direct application of the novel detection system in the present invention, modifications have been added to two

oligonucleotides (listed herein): 5'-TACGGACGGAAACT-3 (SEQ ID NO:3), and 5'-TACGGACAGAAACT-3' (SEQ ID NO:1), both located from position 582 to 595 as referred to the wild type human hepatitis B virus genome. These include a fluorescent dye, 6-(fluorescein-6-carboxamido) hexanoate, at its 5' terminus for microscopic detection and a primary amine group at its 3' terminus allowing its immobilization on solid glass supports. The resulting oligonucleotides that are immobilized on solid glass supports has the following structure: 5'-(6FAM)TACGGACGGAAACTGTTTTTTTTTTTT (C-7 amine)-3'(SEQ ID NO:4), and 5'-(6FAM)TACGGACAGAAACTGTTTTTTTTTTTT (C-7 amine)-3' (SEQ ID NO:5), and the second oligonucleotide contains the mutation G to A (position 8 of the oligonucleotide, in bold) leading to change at amino acid 145 (Glycine to Arginine) of human hepatitis B virus surface antigen. There is also an inclusion of a poly-T (underlined) as a synthetic linker aiming at optimizing the subsequent hybridization reaction with target human viral DNA sequences from serum samples.--

Mark Up Copy of Amendments to the Claims

Claims 20, 21, 26, 29, 30, 35, 36, 39, 41, 43, 44, 46, 47, 48, 49, 50, 52, 53, 54, 57, 58, 59, 60, 61, 62, 64, 65, and 66 have been amended as follows:

--20. (Amended) The oligonucleotide of claim 19, wherein the oligonucleotide comprises the sequence TACGGACGGAAACT (SEQ ID NO:3).--

--21. (Amended) The oligonucleotide of claim 19, wherein the oligonucleotide comprises the sequence TACGGACGGAAACTGTTTTTTTTTTTT (SEQ ID NO:4).--

--26. (Amended) An oligonucleotide which (1) is immobilized, (2) comprises the sequence TACGGACGGAAACTGTTTTTTTTTTTT (SEQ ID NO:4), (3) is linked to 6-(fluorescein-6-carboxamido) hexanoate at its 5' terminus, and (4) is linked to a C-7 amine at its 3' terminus.--

--29. (Amended) The oligonucleotide of claim 27, wherein the oligonucleotide comprises the sequence TACGGACAGAAACT (SEQ ID NO:1).--

--30. (Amended) The oligonucleotide of claim 27, wherein the oligonucleotide comprises the sequence TACGGACAGAAACTGTTTTTTTTTTTT (SEQ ID NO:5).--

--35. (Amended) An oligonucleotide which (1) is immobilized; (2) comprises the sequence TACGGACAGAAACTGTTTTTTTTTTTT (SEQ ID NO:5), (3) is linked to 6-(fluorescein-6-carboxamido) hexanoate at its 5' terminus, and (4) is linked to a C-7 amine at its 3' terminus.--

--36. (Amended) An oligonucleotide which (1) has a sequence which corresponds to a portion of a nucleic acid which encodes human hepatitis B virus surface antigen, wherein the sequence is AGGATCAACAACAACCAGTA (SEQ ID NO:6), and (2) is linked at its 5' terminus to a biotin group.--

--39. (Amended) The oligonucleotide of claim 38, wherein the sequence is ATCGTCCTGGGCTTTCGCAA (SEQ ID NO:7).--

--41. (Amended) The oligonucleotide of claim 38, wherein the sequence is ATCGTCCTGGGCTTTCGCAA (SEQ ID NO:7), and the fluorescent dye is Texas red.--

--43. (Amended) The composition of claim 42, wherein (i) the first oligonucleotide has the sequence AGGATCAACAACAACCAGTA (SEQ ID NO:6); and (ii) the second oligonucleotide has the sequence ATCGTCCTGGGCTTTCGCAA (SEQ ID NO:7), and the fluorescent dye is Texas red.--

--44. (Amended) A method for identifying a human hepatitis B virus surface antigen mutant 145 in a sample which comprises:

(A) obtaining viral nucleic acid from a sample;

(B) amplifying the viral nucleic acid in a polymerase chain reaction using two primers, wherein

(1) one primer is [an] a first oligonucleotide which (i) has a sequence which corresponds to a portion of a nucleic acid which encodes human hepatitis B virus surface antigen, and (ii) is linked at its 5' terminus to a biotin group; and

(2) the other primer is [an] a second oligonucleotide which (1) has a sequence which is complementary to a nucleic acid which

encodes human hepatitis B virus surface antigen, and (2) is linked at its 5' terminus to a fluorescent dye;

(C) obtaining, from the amplified nucleic acid, single stranded nucleic acid which comprises the fluorescent dye;

(D) contacting the single stranded nucleic acid which comprises the fluorescent dye to an immobilized third oligonucleotide, which oligonucleotide comprises a sequence which (i) corresponds to a portion of a human hepatitis B virus surface antigen nucleic acid, which portion comprises a mutation present in a mutant human hepatitis B virus, (ii) is linked to a fluorescent dye at its 5' terminus; and (iii) is linked to a primary amine group at its 3' terminus, under conditions permitting hybridization between the single stranded nucleic acid which comprises the fluorescent dye and the third oligonucleotide,

wherein hybridization between the single stranded nucleic acid which comprises the fluorescent dye and the immobilized third oligonucleotide identifies the sample as one containing a human hepatitis B virus surface antigen mutant 145.--

--46. (Amended) The method of claim 44, wherein the third oligonucleotide comprises the sequence TACGGACAGAAACT (SEQ ID NO:1).--

--47. (Amended) The method of claim 44, wherein the third oligonucleotide comprises the sequence TACGGACAGAAACTGTTTTTTTTTTTT (SEQ ID NO:5).--

--48. (Amended) The method of claim 44, wherein the fluorescent

dye which is linked to the third oligonucleotide is 6-(fluorescein-6-carboxamido) hexanoate.--

--49. (Amended) The method of claim 44, wherein the primary amine group which is linked to the third oligonucleotide is a C-7 amine.--

--50. (Amended) The method of claim 44, wherein the third oligonucleotide is immobilized on a solid support.--

--52. (Amended) The method of claim 44, wherein the third oligonucleotide (1) is immobilized, (2) comprises the sequence TACGGACAGAAACTGTTTTTTTTTTT (SEQ ID NO:5), (3) is linked to 6-(fluorescein-6-carboxamido) hexanoate at its 5' terminus, and (4) is linked to a C-7 amine at its 3' terminus.--

--53. (Amended) The method of claim 44, wherein the primer in step (B)(1) has the sequence AGGATCAACAACAACCAGTA (SEQ ID NO:6).--

--54. (Amended) The method of claim 44, wherein the primer in step (B)(2) has the sequence ATCGTCCTGGGCTTTCGCAA (SEQ ID NO:7).--

--57. (Amended) A method for identifying a wildtype human hepatitis B virus surface antigen in a sample which comprises:

(A) obtaining viral nucleic acid from a sample;

(B) amplifying the viral nucleic acid in a polymerase chain reaction using two primers, wherein

(1) one primer is [an] a first oligonucleotide which (i) has a sequence which corresponds to a portion of a nucleic acid which encodes

human hepatitis B virus surface antigen, and (ii) is linked at its 5' terminus to a biotin group; and

(2) the other primer is [an] a second oligonucleotide which (1) has a sequence which is complementary to a nucleic acid which encodes human hepatitis B virus surface antigen, and (2) is linked at its 5' terminus to a fluorescent dye;

(C) obtaining, from the amplified nucleic acid, single stranded nucleic acid which comprises the fluorescent dye;

(D) contacting the single stranded nucleic acid which comprises the fluorescent dye to an immobilized third oligonucleotide, which oligonucleotide comprises a sequence which (1) corresponds to a portion of a wildtype human hepatitis B virus surface antigen nucleic acid, (2) is linked to a fluorescent dye at its 5' terminus; and (3) is linked to a primary amine group at its 3' terminus, under conditions permitting hybridization between the single stranded nucleic acid which comprises the fluorescent dye and the third oligonucleotide,

wherein hybridization between the single stranded nucleic acid which comprises the fluorescent dye and the third oligonucleotide identifies the sample as one containing a wildtype human hepatitis B virus surface antigen.--

--58. (Amended) The method of claim 57, wherein the third oligonucleotide comprises the sequence TACGGACGGAAACT (SEQ ID NO:3).--

--59. (Amended) The method of claim 57, wherein the third

oligonucleotide comprises the sequence TACGGACGGAAACTGTTTTTTTTTTT (SEQ ID NO:4).--

--60. (Amended) The method of claim 57, wherein the fluorescent dye which is linked to the third oligonucleotide is 6-(fluorescein-6-carboxamido) hexanoate.--

--61. (Amended) The method of claim 57, wherein the primary amine group which is linked to the third oligonucleotide is a C-7 amine.--

--62. (Amended) The method of claim 57, wherein the third oligonucleotide is immobilized on a solid support.--

--64. (Amended) The method of claim 57, wherein the third oligonucleotide (1) is immobilized; (2) comprises the sequence TACGGACGGAAACTGTTTTTTTTTTT (SEQ ID NO:4); (3) is linked to 6-(fluorescein-6-carboxamido) hexanoate at its 5' terminus, and (4) is linked to a C-7 amine at its 3' terminus.--

--65. (Amended) The method of claim 57, wherein the primer in step (B)(1) has the sequence AGGATCAACAACAACCAGTA (SEQ ID NO:6).--

--66. (Amended) The method of claim 57, wherein the primer in step (B)(2) has the sequence ATCGTCCTGGGCTTTCGCAA (SEQ ID NO:7).--